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SPECIFICATION

A NON-INVASIVE BLOOD CONSTITUENT MEASURING INSTRUMENT AND MEASURING METHOD

FIELD OF THE INVENTION

The present invention relates to an instrument and a method for measuring blood biochemical constituent including blood glucose concentration and, more particularly, to a non-invasive blood constituent measuring instrument and a method for measuring blood glucose concentration without sampling blood from a living body.

In the modern era of the expanding aged society as well as the change in life-style, there has been a considerable increase in the number of diabetes which is growing social concern as a representative of lifestyle-related diseases. It is so far a general practice to measure blood glucose concentration by sampling a small amount of blood. However, it is strongly desired to reduce pain and botheration associated with the blood sampling. In addition, there is no other method available than the blood examination for measuring blood biochemical constituent.

On the other hand, a non-invasive measurement using near infrared light is collecting attentions for extremely low risk to living bodies and the possibility for

measurement of items so far impossible by existing measuring methods. For example, glucose has an inherent absorption band derived from its constituents in this wavelength band and various methods are reported (Reference Literature: Ozaki Yukihiro, Practical Spectroscopy Series No. 4 "Medical Application of Spectroscopy", IPC (Industrial Publishing Consulting, Inc.)

For example, according to the reference literature, a method to obtain blood glucose concentration by irradiating an infrared light to a fingertip and through the computation of its transmitted light by a computer is proposed. For this method, however, it is very difficult to estimate glucose concentration in blood from the transmitted light obtained and thus a method to estimate glucose concentration using a multi-regression analysis is also proposed.

However, the absorption band inherent to glucose in the near infrared range overlaps on other constituent absorption ranges of protein materials, etc. and it is difficult to separate an absorption characteristic coming from glucose only and absorption characteristic of other material and therefore, there is a question in measuring accuracy and reproducibility of measurement and the proposed method is not yet put in practical use.

Further, a glucose measuring method using the above-mentioned multi-regression analysis is reported in

the above-mentioned reference literature as shown below. That is, this method is to measure glucose in blood serum using the PLS method (partial least squares analysis) that is one of chemometrics by measuring infrared spectrum with lights in two wavelength ranges of 1325 ~ 1800 nm and 2035 ~ 2375 nm applied to glucose sample melted in blood serum.

However, as reported that a near infrared spectroscope made by NIR System Corp. according to the transmission penetration method using a quartz photocell in 0.5 mm light path length in the measurement, a quartz photocell was used in the measurement and is not a non-invasive measurement by irradiating light to living bodies.

In a non-invasive blood glucose concentration measuring method using a conventional absorption analysis method, the glucose absorption band overlaps the absorption ranges of other biological tissues in living bodies such as bones, veins, muscles and it is difficult to separate the ranges and the accurate measurement is not feasible and is therefore not put in practical use.

Accordingly, an objective of the present invention is to provide a non-invasive blood glucose measuring instrument and a measuring method by solving the above-mentioned problems to allow the blood glucose concentration measurement with a simple way as well as with high accuracy.

SUMMARY OF THE INVENTION

A non-invasive blood constituent measuring instrument according to an embodiment of the present invention includes a light source to irradiate a light having plural wavelengths to a living body; a light detector to detect the light transmitted through a living body or reflected therefrom; an instantaneous spectrum analyzer to analyze spectrum of light transmitted through or reflected on the living body at different times when the output signal of the light receiver is supplied; a spectrum subtraction generator to generate spectrum subtraction from light spectrum at the different times measured by the spectrum analyzer; and a blood constituent predictor into which output data of the spectrum subtraction is input and blood constituent is output.

Further, in the non-invasive blood constituent measuring instrument according to the embodiment of the present invention, a blood constituent predictor is provided with a multi-regression analyzing model using plural spectrum data of whole blood constituent of which is known as an explanatory variable and using the blood constituent as an objective variable, wherein being input the spectrum subtraction data obtained from the blood of which blood constituent is known as the explanatory variable, the multi-regression analyzing model computes the object variable and outputs this objective variable

as a blood constituent.

Further, the non-invasive blood glucose concentration measuring instrument according to the embodiment of the present invention is composed of a light source to irradiate a light containing plural wavelengths; a light detector to detect the light transmitted through a living body or reflected therefrom; an instantaneous spectrum analyzer to which the output signal of the light receiver is supplied and which analyzes spectrum of the light transmitted through the living body or reflected therefrom at different times; a spectrum subtraction generator to generate spectrum subtraction from the spectrum of the light measured by the spectrum analyzer at the different times; and a blood glucose concentration predictor into which the output data of the spectrum subtraction generator is input and which outputs the blood glucose concentration.

Further, in the non-invasive blood glucose concentration measuring instrument according to the embodiment of the present invention, the blood glucose concentration predictor is constructed with a multi-regression analyzing model into which spectrum subtraction data of plural whole blood samples of known blood constituent is input as the explanatory variable and in which the blood glucose concentration is computed as an objective variable and output as blood glucose concentration.

A non-invasive blood constituent measuring method according to an embodiment of the present invention includes the steps of irradiating a light containing plural wavelengths to a living body; detecting light transmitted through or reflected from the living body and converting it into an electric signal; analyzing spectrum of the light transmitted through the living body or reflected therefrom at different times using the converted electric signal; generating spectrum subtraction from the spectrum of the light at the different times; and predicting corresponding blood constituents from the spectrum subtraction.

Further, in the steps of the non-invasive blood constituent measuring method according to the embodiment of the present invention, the blood constituent predicting step futher includes the steps of preparing a multi-regression analyzing model, into which spectrum data of plural whole blood samples having known blood constituent is input as an explanatory variable and blood constituent is output as an objective variable, inputting the spectrum subtraction data obtained from blood of which blood constituent is not known as an explanatory variable, and outputting the blood constituent as an objective variable.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a block diagram according to the embodiment of the present invention;

FIG. 2 is a flowchart showing a construction method of an analytical prediction model used in the blood concentration prediction instrument shown in FIG. 1;

FIG. 3 is a diagram showing an arterial pulsatile volume waveform in a living body;

FIG. 4 is a waveform diagram showing examples of spectrums output from an instantaneous spectrum analyzer in FIG. 1;

FIG. 5 is a diagram for explaining the operation of a blood glucose prediction instrument shown in FIG. 1;

FIG. 6 is a diagram showing properties of the light passed through a living body for explaining the principle of the present invention; and

FIG. 7 is a diagram showing another embodiment of the non-invasive blood glucose concentration measuring instrument according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

An embodiment of the present invention will be described below in detail referring to the attached drawings. In the embodiment shown below, the concentration measurement of blood glucose as one of blood constituents will be explained. However, the present invention is also applicable to the concentration measurement of such other materials as glycol-albumin, hemoglobin A_{1C}(HbA_{1C}), cholesterol and so on, which are blood constituents other

than blood glucose existing in the arterial blood having light absorption characteristics and scattering as well as reflecting characteristics.

FIG. 1 is a block diagram showing a non-invasive blood glucose concentration measuring instrument of the present invention.

As shown in FIG. 1, the light source 11 to emit a light having a near infrared wavelength range of, for example, 800 ~ 2400 nm wavelength has been installed in a non-invasive blood glucose concentration measuring instrument. The light emitted from the light source 11 is irradiated to a living body 13 such as a fingertip, an ear lobule, etc. through an active spectroscope 12. The active spectroscope 12 separates light emitted from the light source 11 sequentially over its whole wavelength range at an interval of, for example, 3 nm and sequentially outputs about 530 number of lights having a diferent wavelength. The scanning of the wavelength by the active spectroscope 12 in the above-mentioned wavelength range is executed repeatedly about 20 times or more in one cycle time of the arterial volume waveform in the living body 13. In other words, the active spectroscope 12 transmits the lights in a near infrared range sequentially at an interval of about 50 ms or less and irradiates them to the living body 13. The light passed through the living body 13 is detected by a light detector arranged at the opposite side of the

light source 11 and is converted into an electric signal.

An output signal of the light detector 14 is supplied to an instantaneous spectrum analyzer 15, wherein an absorption spectrum obtained as an output of the light detector 14 for each wavelength of the light source 11 is produced. That is, the output from a sensor 16 that detects an intensity of the light incident to the living body 13 from the light source 11, that is, an intensity of the incident light I^{λ}_{o} with each wavelength (λ) is supplied with the output signal of the light detector 14 to the spectrum analyzer 15. As described later, the intensity of light (I^{λ}) with each wavelength (λ) passed through the living body 13, that is, an absorbance (OD^{λ}) which is a ratio of the logarithmic intensity of passed light I^{λ} to that of the incident light I^{λ}_{o} ($OD^{\lambda}=\log I^{\lambda}_{o} / I^{\lambda}$) is computed here and an absorption spectrum is produced. Twenty (20) number of the absorption spectrums are produced per second by twenty (20) times of scanning per second of the active spectroscope 12 as described above.

The absorption spectrum data obtained by the spectrum analyzer 15 is stored in a spectrum data memory 17. The spectrum data memory 17 stores and maintains output data for several seconds of the spectrum analyzer 15 sequentially on the first-in first-out basis.

Spectrum data read from the spectrum data memory 17 is supplied to a subtraction processor 18 and a spectrum

subtraction ($OD^{\lambda}_{ti'}-OD^{\lambda}_{ti}=\Delta OD^{\lambda}_{ti}$), which is composed of a difference in absorbance in corresponding wavelengths (λ) between the absorption spectrums (OD^{λ}_{ti}) at different times (ti) is produced as described later. From this subtraction technique, the subtraction data (ΔOD^{λ}_{ti}) include only information of arterial blood without the other biological tissue components such as skin, bones, muscles etc, as also described later.

The spectrum analyzer 15, the spectrum data memory 17 and the subtraction processor 18 are operated in sync with the 20 times scanning per second of the active analyzer 12. The synchronization between these units is made by a timing device 19 to supply a synchronizing signal to them.

The spectrum subtraction data (ΔOD^{λ}_{ti}) produced by the subtraction processor 18 is stored in a spectrum subtraction memory 20. The spectrum subtraction memory 20 also stores the output data of the subtraction processor 18 for several seconds sequentially on the first-in first-out basis. It is noted, as described later, that the subtraction data ΔOD^{λ}_{ti} is mathematically derived to be equal to the change in the intensity of the transmitted light ($I^{\lambda}_{ti'}-I^{\lambda}_{ti}=\Delta I^{\lambda}_{ti}$) divided by the intensity of the light at the time ti (I^{λ}_{ti}), provided that ΔI^{λ}_{ti} is very small, that is, $\Delta OD^{\lambda}_{ti}=\Delta I^{\lambda}_{ti} / I^{\lambda}_{ti}$. This means that the light intensity and its change are needed in practical use without detection of the intensity of the incident light (I^{λ}_{o}).

The spectrum subtraction data read out of this spectrum subtraction memory 20 is input into a blood glucose predictor 21. The blood glucose predictor 21 is a device to predict blood glucose concentration through the multi-regression analysis using the PLS (Partial Least Squares Regression) method that is one of multi-regression analyses from input spectrum subtraction data. That is, the blood glucose predictor 21 is constructed as a software model to compute the blood glucose concentration according to the PLS method using whole blood samples that have many known blood glucose concentrations.

FIG. 2 is a flow chart showing a method for constructing the blood glucose predictor 21 as the software model shown in FIG. 1. Known blood glucose concentration samples 31 are the whole blood samples filled in plural quartz photo-cells whose glucose concentrations are known and are slightly differrnt from each other. These samples 31 were taken directly from, for example, seven healthy adult males and were made the plural whole blood samples having different albumin or hematocrit concentrations from other blood samples by 18 mg/dl like 36, 54, ... 486 mg/dl in the glucose concentration range 30 ~ 450 mg. These samples 31 are analyzed by a spectroscopic analyzer composed of the light source 11, the spectroscope 12, the lightdetector 14 and the spectrum analyzer 15, and thus a absorption spectrum 32 is prepared. A PLS regression analysis

prediction model 34 is determined by data X consisting of these absorption spectrum 32, together with corresponding known n number of blood glucose concentrations (yn) 33. That is, data X consisting of the absorption spectrum 32 is an absorbance for different m (about 530 waves) number of the spectroscopic waveforms. Expressing these absorbance with x_1, x_2, ..., x_m, the known n number of blood glucose concentrations y1, y2, ..., yn are approximated by the following determinant using these variables:

$$\begin{pmatrix} y1 \\ y2 \\ \\ \\ yn \end{pmatrix} = \begin{pmatrix} a11 & \cdots\cdots & a1n \\ & & \\ & & \\ & & \\ a1n & \cdots\cdots & ann \end{pmatrix} \begin{pmatrix} X1 \\ \\ \\ \\ Xn \end{pmatrix} \qquad \text{Formula 1}$$

A coefficient of this determinant is determined using the PLS method by substituting the absorption spectrum data using the above-mentioned sample solution into the determinant. A blood glucose prediction model formula is thus obtained. Here, the PLS method is a technique to consider the correlation of potential variables T_{PLS} as explanatory variables and to utilize data contained in X as many as possible.

$$\left.\begin{aligned} y &= Tq + f \\ X &= TPt + E \\ S &= ytT \end{aligned}\right\} \qquad \text{Formula 2}$$

where, T: Potential variable

q: Potential variable regression coefficient

E, f: Residual of X, y

P: Loading matrix

S: Covariance of $_y$ and T

P of the determinant 2 and regression coefficient q of potential variable T are determined by inputting blood glucose y_1, y_2 , ...y_n of n known blood glucose samples into a regression analytical computer application software (for example, Trade Name: MATLAB) according to the PLS method available in the market. Thus, the regression analysis prediction model (blood glucose computing model) according to the PLS method is obtained. Then, a new T is computed based on P that is determined when a model is prepared, when new absorbance of respective spectroscopic wavelengths x_1, x_2,..., x_m obtained from blood of which blood glucose concentration is unknown are input as data. These new absorbance of respective spectroscopic wavelengths x_1, x_2, ..., x_m are input as spectrum subtraction data read from the above-mentioned spectrum subtraction memory 20. Using this new T and q determined when a model was prepared, a blood glucose prediction value y_i is obtained.

Next, the operations of the non-invasive blood glucose concentration measuring instrument thus constructed according to the embodiment of the present invention and the blood glucose measuring procedures will be explained

referring to FIG. 3 and FIG. 4.

As shown in FIG. 1, the light emitted from the light source 11 is spectroscopically scanned over the wavelength range by the active spectroscope 12 at a rate of, for example, 20 times per second and is irradiated to the living body 13. The light transmitted through the living body 13 is detected by the light detector 14 and each absorption spectrum is measured by the spectrum analyzer 15 at an intervals of 40 ~ 50 ms. The spectrum data thus measured is stored in the spectrum memory 20 until the next spectrum measuring time. FIG. 3 shows the arterial pulsatile volume waveform in the living body 13, the horizontal axis shows time and the vertical axis shows arterial blood volume change (pulsatile volume waveform). Time t_1, t_2, ..., t_n in FIG. 3 show the time when the scanning of the wavelength starts by the active spectroscope 12, where n is 20 in this case. Absorption spectrum at the time t_1, t_2, ..., t_n thus obtained are shown in FIG. 4, where the horizontal axis shows the wavelength(λ) and the vertical axis shows absorbance($OD^{\lambda}{}_{ti}$; ti=t1, t2, ---, tn).

Next, the spectrum subtraction processor 18 shown in FIG. 1 produces a spectrum subtraction from absorption spectrums at two any optional times, for example, a time t_1 and a peak time t_m in the arterial pulsatile volume waveform selected from the times t_1, t_2, ..., t_n.

FIG. 5 is a diagram for explaining an operation of the

blood glucose predictor 21 shown in FIG. 1. One example of the above-mentioned spectrum subtraction is shown in FIG. 5(a). The horizontal axis in FIG. 5 shows the wavelength(λ) and the vertical axis shows a difference in the absorbance(ΔOD^{λ}_{ti}). The curved line indicating the spectrum subtraction is a plotted difference in the absorbance at respective wavelengths of absorption spectrum, for example, at t_3 and t_6 in this case.

Graphes (S1), (S2), ..., (Sm) in FIG. 5 show absorption spectrums of m number of whole blood samples of known blood glucose concentration.

Spectrum subtraction data shown in FIG. 5(a) are input to the blood glucose concentration predictor 21. Further, a PLS regression analytical model is incorporated in the blood glucose concentration predictor 21. The PLS regression analytical model is a numerical expression showing the relation between absorption spectrums of m number of whole blood samples (S1), (S2), ..., (Sm) shown in FIG. 5 each having known blood glucose concentration and the known blood glucose concentrations corresponding to the samples. The blood glucose concentration predictor 21 compares the spectrum subtraction given from the spectrum subtraction memory 20 as input data with each of the absorption spectrums of the sample solutions and outputs the blood glucose concentration of the sample solution having the most similar absorption spectrum as

a predicted blood glucose concentration.

Thus, it is revealed that a blood glucose concentration can be predicted at a high level of accuracy when spectrum subtraction is used as input data to the blood glucose concentration predictor 21. The reason will be explained referring to FIG. 6. FIG. 6 is a schematic diagram showing the relation of the intensity of incident light I^{λ}_{o}, the intensities of transmitted lights I^{λ}_{1}, I^{λ}_{2} and absorption amount in the living body 13 at the wavelength λ. The arterial blood volume waveform P as shown in FIG. 3 is also shown in FIG. 6. In FIG. 6, for example, the transmitted light intensity I^{λ}_{1} (Incident light intensity I^{λ}_{o}) at $t = t_1$ where the arterial blood volume waveform P becomes minimal is (Incident light intensity I^{λ}_{o}) - (Absorption light intensity in the arterial blood layer at the minimum volume change I^{λ}_{3}) - (Absorption light intensity in the venous blood layer I^{λ}_{4}) - (Absorption light intensity in the biological tissues excluding blood I^{λ}_{5}); that is, $I^{\lambda}_{1} = I^{\lambda}_{o} - (I^{\lambda}_{3} + I^{\lambda}_{4} + I^{\lambda}_{5})$ at t=t1. Further, the transmitted light intensity I^{λ}_{2} at $t = t_m$ where the volume change in the artery becomes maximal is (Incident light intensity I^{λ}_{o}) - (Absorption light intensity in the arterial blood layer of the maximum volume change I^{λ}_{6}) - (Absorption light intensity in the venous blood layer I^{λ}_{4}) - (Absorption light intensity in the biological tissues excluding blood I^{λ}_{5}), that is, $I^{\lambda}_{2} = I^{\lambda}_{o} - (I^{\lambda}_{6} + I^{\lambda}_{4} + I^{\lambda}_{5})$ at t=tm. The

differences of these two transmitted light intensities(I^{λ}_1-I^{λ}_2) extract the spectrum of pulsative element ΔI^{λ} that is the pulsating absorption intensity of the artery(I^{λ}_1-I^{λ}_2= I^{λ}_6-I^{λ}_3=ΔI^{λ}). Although the absorption light spectrum in the spectrum analyzer 15 or the spectrum data memory 17 shown in FIG. 1 contains the absorption light element in the venous blood and biological tissues excluding blood, the spectrum subtraction(ΔOD^{λ}) generated in the spectrum subtraction processor 18 becomes the light absorption spectrum depending on the light absorption element of arterial blood absorption element only. Because the subtraction(ΔOD^{λ}) from the absorbance at t=t1($OD^{\lambda}1$=log I^{λ}_o / I^{λ}_1) to that at t=tm($OD^{\lambda}2$=log I^{λ}_o / I^{λ}_2) is equal to log I^{λ}_2/ I^{λ}_1(=log(I^{λ}_1-ΔI^{λ})/ I^{λ}_1=log(1-ΔI^{λ}/ I^{λ}_1), and thus ΔOD^{λ} is nearly equal to -ΔI^{λ}/ I^{λ}_1 when $\Delta I^{\lambda} \ll I^{\lambda}_1$ ($\Delta OD^{\lambda} \simeq -\Delta I^{\lambda} / I^{\lambda}_1$). Accordingly, this subtraction does not contain the absorption element by the venous blood and biological tissues excluding blood. Therefore, it becomes possible to eliminate influence of these interfering factors and to put into practical use of a highly precise non-invasive blood glucose concentration measuring instrument.

By the way, in producing the spectrum subtraction(ΔOD^{λ}) by the measurement of living body 13 described above, when a difference in arterial spectrum waveforms that become the maximum and minimum volume changes in one heart

beat, the blood glucose concentration is computed at one time per one heart beat and the blood glucose concentration is output at one time per one heart beat. However, as spectrum data is measured repetitively nearly 20 times in one heart beat, it is possible to take out spectrum subtraction at two adjacent times as continuous spectrum subtractions while shifting times sequentially and compute blood glucose concentrations using these continuous spectrum subtractions. In this case, it is expected that a change in spectrums at adjacent times is very little, signal noise ratio of spectrum subtraction drops and a fluctuation (a residual error) of the result of blood glucose concentration computation may become large. Accordingly, it is also possible to display the measured result easy to look by inputting the result into the blood glucose concentration predictor 21 by executing the time series average of these spectrum subtractions or by smoothing successively computed blood glucose concentrations through the statistical procedure such as the time average or moving average by the blood glucose concentration predictor 21.

Further, in the embodiment described above, the transmitted light spectrum from the living body 13 is measured but the reflected light from the living body 13 may be measured other than the transmitted light.

FIG. 7 is a partial explanatory diagram showing this

embodiment, in which the same composed elements as those in FIG. 1 are assigned with the same reference numerals and the detailed explanation thereof will be omitted. In this embodiment, the light detector 14 is arranged at the same side as the light source 11 to the living body 13 as illustrated and detects the reflected light from the living body 13. By supplying the output signal of the light detector 14 to the spectrum analyzer 15 shown in FIG. 1, it is possible to measure blood glucose concentration likewise the embodiment described above.

Further, in the embodiments shown in FIG. 1 and FIG. 7, the light from the light source 11 is separated by the active spectroscope 12 and then irradiated to the living body 13. However, the transmitted light or reflected light may be separated for spectrum analysis after the light from the light source 11 is irradiated to the living body 13. For example, the light can be separated by an array of plural light detectors each having a sensitivity only for specific wavelengths (λ).

Further, in the embodiments described above, a model applied with the PLS method is used as the blood glucose concentration predictor 21. However, a model according to the principal constituents regression shown in Formula 3, which is one of multi-regression analyses may be used. The regression analysis blood glucose concentration computing model that is constructed using the PCR method is expressed

by the following Formula 3.

$$\left.\begin{aligned} Y &= Tb + f \\ &= t_1b_1+t_2b_2+ \ldots +t_nb_n \end{aligned}\right\} \quad \text{Formula 3}$$

where, T: Principal constituents score

b: Principal constituents score regression coefficient

That is, a multi-regression analysis blood glucose concentration computing model is constructed by corresponding a known blood glucose concentration of the whole blood sample 31 to an objective variable y, applying spectrum data of the whole blood sample 31 to an explanatory variable x and deciding a multi-regression analysis blood glucose concentration computing model. When spectrum subtraction data of an unknown blood glucose concentration is input into the blood glucose concentration predictor 21 in which this principal constituents score regression coefficient b is set, a blood glucose concentration predict value ya is computed and output.

Further, when developing a regression analysis prediction model (a blood glucose concentration computing model) in the above-mentioned embodiment, the sample 31 having a known blood glucose concentration is filled in plural quartz cells and absorption spectrum data X1, X2, ... Xm are developed with a spectroscopic analyzer comprising the light source 11, the spectroscope 12, the light receiver 14 and the spectrum analyzer 15. However, for these

absorption spectrum data X1, X2, ..., Xm, spectrum subtraction data obtained with units ranging from the light source 11 to the spectrum subtraction memory shown in FIG. 1 using plural living bodies of which blood glucose concentrations are known can be used.

Further, in the embodiment mentioned above, the measurement of blood glucose concentration is shown. However, regarding the measurement of concentration of another material having absorption characteristics and scatter reflection characteristics existing in the arterial blood, it is possible to predict and compute the concentration of that material existing in the arterial blood similarly. That is, it is possible to predict and compute the concentration by measuring spectrum of wavelength band corresponding to the absorption characteristics or the reflecting characteristics of the material and deciding the regression coefficient of the multi-regression analyzing model using the PLS method or the PCR method referring to a concentration of a sample of that is the standard of that material using the same system and procedures shown in the above embodiment.

As described above, with the non-invasive blood constituent measuring instrument and the method according to the embodiment of the present invention, it is possible to measure blood constituents in a living body by irradiating near infrared light to a finger tip, etc.

quickly and highly precisely without feeling pain and burden involved in the blood drawing.

Further, according to the embodiment of the present invention, spectrum subtraction using the arterial blood beat is used as described above. However, the spectrum subtraction analysis may be made by generating the venous blood volume change in the biological tissues using such a method as the venous occlusion method, for example. Thus, the adverse effect of other biological tissue constituents is eliminated and blood constituent can be measured at a highly precise and sensitive level.